REMARKS

Status of the Claims.

Claims 1, 3-15, 34-44, and 53-54 are pending with entry of this amendment, claims 16-22 being cancelled and no claims being added herein. Claim 34 is amended there to correct claim dependency in view of the claim cancellation.

Oath/Declaration.

Applicants note that the Examiner alleged that the present Oath/Declaration is defective and requested a substitute Oath/Declaration. Per the Examiner's request, Applicants are presently obtaining a substitute declaration and will provide such when the document is executed.

35 U.S.C. §112, first paragraph.

The rejection of claim 3-13, 16-20, 34-42, and 53-54 under 35 U.S.C. §112, first paragraph, was maintained. In particular, the Examiner alleged that the response did not adres sthis rejection. The examiner further alleged that the claims still encompass antibodies with conservative substitutions, 70% identity and affinity of only 10 mM, and antibodies with no more than 30 residue differences wherein the alterations substitutions or differences can be in the CDRs. Applicants respectfully traverse.

In maintaining his rejection, the Examiner in effect simply asserts that Applicants have not altered the scope of the pending claims. **The Examiner, however, fails to address the substantive arguments provided in the previous response explaining why the pending claims are fully enabled.** Contrary to the Examiner's assertion, the previously filed response expressly addressed all of the points raised by the Examiner.

In particular, the Examiner previously alleged that:

1) "It is unclear than an antibody that contains one, two, or three CDR would bind antigen as claimed" (office Action, page 3)

2) "The specification "does not enable the myriad of antibodies encompassed by claim 4 which recites an antibody that is 70% sequence identity with SEQ ID NO:1 or 2 that would bind to the c-erbB2 on cells with an affinity of at least 10 mM. (Office Action, pages 3-4).

3_ It is not clear if an antibody that comprises at least 10 contiguous amino acids (which can be framework residues) from the polypeptide as set forth in SEQ ID NO:1 or 2 would bind specifically to the c-erbB2 receptor as claimed in claim 16" (Office Action, page 4).

The examiner is reminded that he **must treat as true** a statement of fact made by an applicant in relation to an asserted utility, unless **countervailing evidence** can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. [emphasis added] (Official Gazette, 66(4): 1099)

As stated by the Federal Circuit court of Appeals:

> . . . a specification disclosure which contains a teaching of the manner and process of using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patened *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doub the objective truth of the statements contained therein. . . *Ex parte Sudilovsky* 21 USPQ2d 1703 (Fed. Cir., 1992) *citing In re Marzocchi*, 169 USQP 367 (CCPA 1971).

In the instant case, the Examiner argues that it is unclear that the claimed antibody would bind to the c-erbB2 receptor as claimed. **The Examiner, however, has failed to provide any objective evidence whatsoever in support of this assertion.**

Moreover, as previously explained, in making this rejection **the Examiner improperly ignores limitations of the recited claims**. For example, the base claim (claim 1) expressly recites:

> 1. A single chain antibody that **specifically binds to a c-erbB2 receptor**, wherein said antibody **specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1** (SEQ ID NO:2), and further **wherein said antibody is an internalizing antibody**.

If an antibody does not specifically bind to a c-erbB2 receptor at the recited epitope or is not an internalizing antibody, then such antibody is not within the literal scope of the claimed invention (*i.e.*, in effect the claims expressly exclude inoperable embodiments). In other words, Applicants claims only literally read on antibodies that specifically bind to the c-erbB2 receptor as indicated, and Applicants have clearly taught "how to use" such antibodies.

The Examiner is also reminded that a claim need not exclude possible inoperable embodiments. As stated by the PTO Board of Appeals:

> It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination. *Ex parte* Cole, 223 USPQ 94 (BPAI 1983)

Similarly, the Federal Circuit has stated that

> It is not the function of claims to specifically exclude either possible inoperative substances or ineffective reactant proportions. *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46 (CCPA 1974)

For a proposed claim to be unpatentable, the law requires that the number of inoperable embodiments be significant in numbers **and not readily ascertained** by those of skill. *In re Cook and Merigold*, 169 USPQ 298, 301-302 (CCPA, 1971).

In the present case **inoperable embodiments are readily ascertained** by one of ordinary skill in the art and are **expressly excluded** by the claims. The Examiner himself, has admitted that "it is known in the art how to make (1) substitutions within an antibody sequence, (2) calculate 70% identity of one sequence to another, and (3) produce a protein that contains one or two CDRs" (Office Action, page 3, lines 14-16).

Moreover, **the Federal Circuit, in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) expressly held that it was not** undue experimentation to screen large numbers of hybridomas for particular desired monoclonal antibodies. As stated by the Court:

> Enablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "[T]he key word is 'undue' not 'experimentation'. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the instant case, Applicants have created an antibody library comprising 7×10^9 members (*see, e.g.,* page 59, line 19). Clearly, Applicants have taught how to make an enormous library. Screening such a library for specific internalizing c-erbB2 antibodies requires at most routine experimentation. Accordingly, the rejection of claims 3-13, 26-22, 34-44, and 53-54 under 35 U.S.C. §112, first paragraph, should be withdrawn.

If it is the Examiner's position that the antibodies recited in claims 3-13, 26-22, 34-44, and 53-54 **would not function** as claimed (*i.e.* that no antibody meeting the limitations of these claims would specifically bind c-erbB2 as recited) then the Examiner should properly make a utility rejection under 35 U.S.C. §101.

Applicants note, however that, under the new Utility Guidelines, to meet the utility requirement, the invention must provide a **specific**, **substantial** and **credible** utility (*see,* Federal Register, 66(4): 1092-1099). In the instant case, the Examiner's concerns would go to "credible utility". Under the Patent Office's own guidelines:

> A rejection based on lack of utility **should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record**. Office personnel are reminded that **they must treat as true a statement of fact made by an applicant in relation to an asserted utility**, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. [emphasis added] (Federal Register, 66(4): 1098-1099)

In the instant case, the Examiner has failed to establish that "that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement" (*i.e.,* that one of ordinary skill in the art would believe that there exist no operable embodiments corresponding to claims).

Thus, for example, claim 8, recites:

> 8. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining region (CDRs) of SEQ ID NO: 1.

This claim does not limit the antibody to two CDRs. Rather, this claim requires that the antibody include two CDRs of SEQ ID NO:1. One of ordinary skill in the art would readily appreciate that antibodies exist and can readily be made that **comprise** at least two CDRs of SEQ ID NO:1 and that specifically bind to c-erbB2 as recited in claim 1 (indeed, such antibodies are illustrated in the specification). Antibodies that do not show such binding specificity are effectively excluded by the claim language. The Examiner has failed to establish that the **claimed invention** would not work.

Indeed, the claim scope is exactly commensurate with a specific, substantial and credible utility. The Examiner has thus failed to make a *prima facie* case under 35 U.S.C. §112, first paragraph, and/or under 35 U.S.C. §101. Accordingly the rejection of claims 3-13, 16-20, 34-42, and 53-54 on these grounds should be withdrawn.

35 U.S.C. §112, Second Paragraph.

Claims 16-22, 34-44, and 53-54 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 16-22 are canceled with entry of this amendment. In addition claim 34 is amended to refer only to claim 1 thereby obviating this rejection.

Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

35 U.S.C. §103(a).

Claims 1, 34-38, and 53-54 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Xu *et al.* (1993) *Int. J. Cancer*, 53: 401-408, further in view of Bird *et al.* (1988) *Science*, 242: 423-426 and Chaudhary *et al.* (1990) *Proc. Natl. Acad. Sci. USA*, 87: 1066-1070. Claims 1, 34-38, 53-54 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Maier *et al.* (1991) *Cancer Res.*, 51: 5361-5369, further in view of Bird *et al. supra.* and Chaudhary *et al. supra.* Claims 1, 34-38, and 53-54 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Shawver *et al.* (1994) *Cancer Res.*, 54: 1367-1373, further in view of Bird *et al. supra.* and Chaudhary *et al. supra.*

According to the Examiner , Xu *et al.*, Maier *et al.*, and Shawver *et al.* teach hybridomas and antibodies produce from such that are internalizing and bind to c-erbB2. These refer3eces do not teach as single chain antibody or an immunotoxin. The Examiner then relies on Bird *et al.* as allegedly teaching single chain antibodies, and Chaudhary as allegedly teaching single chain immunotoxins. Applicants respectfully traverse.

In effect, the Examiner relies on references teaching **complete antibodies**, and relies on general methods of making to construct an obviousness rejection of the particular claimed single-chain antibodies and chimeric constructs thereof.

The rejection under 35 U.S.C. §103(a) is improper in view of prevailing law. Under Federal Circuit case law, the Examiner must consider the obviousness of the claimed compound in light of the compound(s) identified in the prior art (*i.e.*, **compound must be compared to compound**).

It is improper to consider the method of making in formulating such a rejection. As stated by the Federal Circuit:

> [T]he PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. . . . **We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.** [emphasis added] *Deuel*, 51 F.3d at 1555.

Similarly, in the present case, the claims at issue define compounds (single-chain antibodies), not methods. The Examiner has failed to identify any prior art reference whatsoever that discloses a single-chain antibody specific to c-erbB2. The alleged existence of a general method of making the single-chain antibodies (Bird *et al.*) or the chimeric molecules (Chaudhary *et al.*) **'is essentially irrelevant to the question whether the specific molecules themselves would have been obvious** (*see Bird* supra).

The Examiner's rejection is improperly formulated. The existence of a full length antibody does not render obvious the existence of a particular single chain antibody. The compounds are drastically different in structure. Moverover, the Examiner has failed to even establish that the full-length antibodies identified in Xu *et al.*, Maier *et al.*, and Shawver *et al.* even bind to the recited epitopes.

With respect to the Examiner's comments that it is Applicants burden to establish that the antibodies described by Xu *et al.*, Maier *et al.*, and Shawver *et al.* do not bind to the epitopes recited in the pending claims, Applicants submit that **there is no such burden where the ancillary references (Bird *et al.* and Chaudhary *et al.*) cited by the Examiner do not support a proper obviousness rejecetion under prevailing law.** As explained above, these references, at best, merely provide general methods of making and therefore, under Bell, are insufficient to support an obviousness rejection of particular claimed single-chain antibodies. In view of this, the Examiner has failed to make a proper *prima facie* case under 35 U.S.C. §103(a) and the rejection on these grounds should be withdrawn.

Moreover, in the present case, the Examiner has failed to show how the cited references provide any specific information about the **particular claimed** antibodies. The Examiner is reminded that claim 1 expressly recites:

> 1. A **single chain antibody** that specifically binds to a c-erbB2 receptor, **wherein said antibody specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2)**, and further wherein said antibody is an **internalizing antibody**.

At best, the cited art could be construed as an invitation to prepare a single chain anti-c-erbB2 antibody using phage display methodology. The Examiner's theory that one skilled in the art might be motivated to try to do what Applicants have accomplished amounts to speculation and an impermissible hindsight reconstruction of Applicants' claimed invention.

A general motivation to create an anti-ErbB2 antibody does not necessarily make obvious the specifically-defined antibodies that are subsequently obtained as a result of that search. There is no teaching or suggestion found in Maier *et al.* or Bird *et al.* that would necessarily lead one of skill to an **"antibody specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2)**" or to an **internalizing antibody**.

Indeed application of the general methods disclosed in Bird *et al.* could reasonably lead one of skill in the art to antibodies that bind to any of a number of epitopes other than those bound by F5 or C1. Similarly application of these general methods could easily lead to antibodies that are not internalizing.

While there may have been a general motivation to prepare a single chain anti-ERbB2 antibody, that does not necessarily make obvious the particular antibodies recited in the presently pending claims. Indeed, "obvious to try" is not the standard under 35 U.S.C. §103. **A general incentive does not make obvious a particular result**. *In re Deuel, supra.*

In summary, the fact that one can conceive a general process in advance for preparing an **undefined** compound does not mean that a claimed specific compound or family of compounds was **precisely envisioned** and therefore obvious.

For these reasons as well, the Examiner has failed to make a proper *prima facie* case and the rejection of claims 1, 34-38, and 53-54 under 35 U.S.C. §103(a) should be withdrawn.

Request for a Telephone Interview.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. However, in the Event that the Examiner fails to find the foregoing arguments persuasive, **Applicants expressly request a Telephone Conference (Examiner interview) with the Examiner and his Supervisor.**

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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